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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) **Title:** A COMBINATION OF AN NMDA-ANTAGONIST AND ACETYLCHOLINE ESTERASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

(57) **Abstract:** A pharmaceutical composition comprising (a) an effective amount of one or more of acetylcholinesterase inhibitor(s) or a pharmaceutically effective salt thereof and (b) an effective amount of one or more NMDA-antagonist(s).

A combination of an NMDA-antagonist and acetylcholine esterase inhibitors for the treatment of Alzheimer's disease.

The present invention provides a treatment for mild cognitive impairment (MCI) and for dementia of different types such as dementia of Alzheimer's type, vascular dementia, Lewy body dementia, AIDS dementia and frontotemporal dementia by administration of medicaments having dual mechanisme of action.

Dementia of different origin are a growing problem in the world. Among the elderly, Alzheimer's disease is the most common type of dementia. The prevalence of the disease raises from 2% of the people aged 65-70 to as high as 20% of the people aged 80 and older. Though perhaps not the only contributing factor, the increased life expectancy and the increased elderly population explains the raise in the frequency of the disease.

Alzheimer's disease is a slowly progressing neurodegenerative disease characterised by significant loss of function in more than one cognitive domain. Associated diseases such as psychiatric illness and change in behaviour or personality are common.

Presently, the disease cannot be cured. Current treatment gives for some patients a delay in the symptoms, for others a modest cognitive improvement and a dramatic improvement in only a small number of patients. A slower progression of the disease is also desirable for improving the life quality for the patient and the patient's relatives. However, experience with the current treatment with Alzheimer's therapy, still 30% of the patients do not respond to the treatment. Consequently, a great need for improvement in the treatment of Alzheimer's disease exists.

The mechanisms behind the different types of dementia, including Alzheimer's disease, are not fully understood. Of medicaments available for treatment, which presently is only slowing the progression of the disease, they represent different mechanism of action in the central nervous system.

One group of medicaments are represented by the acetylcholinesterase inhibitors, of which medicaments like Donepezil, Rivastigmine, Galantamine and Tacrine are pharmaceuticals having this particular activity. The acetylcholinesterase inhibitors are presently approved in many countries for treatment of mild to moderate Alzheimer's disease.

Another group of medicaments are the NMDA antagonist of which Memantine is a representative. Memantine was recently approved in the EU for treatment of moderate severe to severe Alzheimer's disease.

Though of very different mechanisms of action, both types of medicaments are useful in the treatment of Alzheimer's disease, though in different stages of the disease progression.

The invention thus provides the combined treatment of a patient suffering from a dementia syndrome with a first component which is an acetylcholinesterase inhibitor(s) and a second component which is an NMDA antagonist.

The invention also provides a pharmaceutical composition which comprises a first component which is an acetylcholinesterase inhibitor(s) and a second component which is an NMDA antagonist.

The acetylcholinesterase inhibitors include, but are not limited to:

Donepezil, a known compound described in EP 296560 and US 4895841.

Galantamines use in the treatment of Alzheimer's disease is described in EP236684 and US 4663318.

Rivastigmine as described in national applications corresponding to US 5602176 and GB 2203040.

Tacrine as used in the treatment of cholinergic deficit state, such as Alzheimer's disease, is described in EP 328535 and US 4816456.

Similarly, when the invention is regarded in its broadest sense, the second component is a compound which functions as an NMDA antagonist or partial antagonist of which assays like Ebert et. al *European Journal of Pharmacology* **1997**, 333 , 99-104 exists for determining this activity. Other compounds than the compounds mentioned here have the desired effect. It is intended to include compounds which show antagonisme in the assay described above.

In the present invention, the combination of one compound of the group of acetylcholinesterase inhibitors with one compound of the group of NMDA antagonist is included. Likewise, the combination of two compounds of the first group with one or two or the compounds selected from the second group is also within the present invention and *vice versa*.

While all combinations of first and second group compounds are useful the following combinations are considered as the preferred combinations:

Memantine/Donepezil, Memantine/Galantamine, Memantine/Rivastigmine and Memantine/Tacrine.

Where the compounds exists as different polymorphs, isomers, enantiomers or tautomers the present invention also embraces these variations as well as different salts or solvates etc.

Active metabolites of the compounds described are also embraced by the invention.

Alzheimer's Disease

Characteristics of Alzheimer's Disease are some of the following symptoms occuring:

- Dementia

- Deficits in cognition (such as language, memory, motor skills and perception ie. aphasia, apraxia, agnosia)
- Progressive worsening of memory and cognitive functions

Some of the following associated symptoms often occur:

Depression, insomnia, incontinence, delusions, illusion, hallucinations, emotional or physical outbursts, shouting, wandering , aggression, agitation, apathy, abnormal eating, sexual disorders and weight loss.

Increased motor tone, myoclonus or gait disorder in the late stages of the disease progression.

Since Alzheimer's disease is not curable at present, the complexity of the disease progression and the associated symptoms often gives rise to a multiplicity of diseases, which all need medical treatment. Such treatment regimens and side-effects are difficult to administerable for the patient as well as for the health carer.

Consequently, a positive outcome of an Alzheimer's treatment is an improved cognitive function. A slower progression of the disease, or a delay in the normal disease progression is a positive outcome of a treatment.

Improvements could also be measured in the secondary or associated symptoms of more psychiatric character. Diminished intake or complete stop in the intake of for example antipsychotic, antidepressive, tranquilising or sedative medication will also be signs of a positive response to the treatment of the underlying cause of the dementia, ie. the Alzheimer's Disease.

When combination treatment is evaluated a synergistic effect of the combined administration could be evaluated and the total dose of the combination treatment of individual compounds relative to the doses used for single compound administration could be lowered.

The present invention covers treatment of mild cognitive impairment and dementia regardless of the underlying cause. For example the dementia can be Alzheimer's disease, vascular dementia, Lewy body dementia, AIDS dementia or frontotemporal dementia.

In the context of this invention, Alzheimer's disease includes all stages of the disease, ie. mild, moderate and severe Alzheimer's disease.

In the context of this invention, mild cognitive impairment are characterised by symptoms defined by Petersen et. al.

Pharmaceutical compositions:

To prepare the pharmaceutical compositions of this invention, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in intimate admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for administration orally, nasal, rectally, percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

Dosage unit form as used in the specification and claims herein refer to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The NMDA antagonist may be administered before, during or after the administration of the acetylcholinesterase inhibitor provided that the time between the administration of the acetylcholinesterase inhibitor and the administration of the acetylcholinesterase inhibitor is such that ingredients are allowed to act synergistically on the CNS.

When simultaneous administration of NMDA antagonist and an acetylcholinesterase inhibitor is envisaged, a composition containing both an acetylcholinesterase inhibitor and an NMDA antagonist may be particularly convenient. The compositions may be prepared as described herein above.

Simultaneous administration may also be accomplished by administration of the active ingredients in two separate unit dosage forms.

When sequential administration of the NMDA antagonist is envisaged, the pharmaceutical composition may comprise, for example, a kit including discrete unit dosage forms containing the NMDA antagonist and discrete unit dosage forms containing an acetylcholinesterase inhibitor, all contained in the same container or pack, e.g. a blister pack.

Dose Ranges

The selection of dosage of the first and second component is that which gives the patient relief of the symptoms of the disease. The dosage depends on several factors such as the potency of the selected compounds, the mode of administration, the age

and weight of the patient, the severity of the condition to be treated and the like. This is considered to be the skill of the artisan and suitable literature can be consulted for the dosages recommended for each compound.

The dosage ranges for the NMDA antagonist, Memantine are 0.1mg –500mg of active ingredient pr. dosage. More preferred are 1- 50 mg and most preferred are 2 - 25 mg. Presently the preferred dosage administered is 20mg.

The dosage of the second component, the acetylcholinesterase inhibitor, will depend on the dosage of the NMDA antagonist administered or vice versa. The average daily dosage of the acetylcholinesterase inhibitor are from 0.1mg –500mg of active ingredient pr. dosage. More preferred are 1- 50 mg and most preferred are 2 - 25 mg. Presently, the dosage regime for the available acetylcholinesterase inhibitor are the following:

Tacrine	10-40 mg four times a day
Donepezil	5-10 mg per day
Rivastigmine	3-12 mg per day
Galantamine	4-24 mg per day

Claims

1. A pharmaceutical composition comprising

(a) an effective amount of one or more of acetylcholinesterase inhibitor(s) or a pharmaceutically effective salt thereof

and

(b) an effective amount of one or more NMDA- antagonist(s)

2. The composition according to claims 1 wherein component (a) is selected from the group consisting of Tacrine, Donepezil, Rivastigmine and Galantamine or mixtures thereof.

3. The composition according to claim 2 wherein component (a) is Donepezil.

4. The composition according to claim 1 wherein component (b) is Memantine.

5. The composition according to claim 1 wherein component (a) and component (b) are in the same delivery vehicle

6. The composition according to claim 1 wherein component (a) and component (b) are in different delivery vehicles.

7. The use of a composition comprising:
(a) an effective amount of one or more acetylcholinesterase inhibitor(s) or a pharmaceutically acceptable salt thereof and
(b) an effective amount of one or more NMDA- antagonist(s) or a pharmaceutically acceptable salt thereof
for the manufacture of a medicament for the treatment of mild cognitive impairment or dementia.

8. The use according to claim 7 wherein dementia is of Alzheimer's type.

9. The use according to claims 7 or 8 wherein component (a) is selected from the group consisting of Tacrine, Donepezil, Rivastigmine and Galantamine and mixtures thereof.

10. The use according to claims 7 -9 wherein component (a) is Donepezil.

11. The use according to claims 7-10 wherein component (b) is Memantine

12. A method for treating mild cognitive impairment or dementia in a mammal comprising administering to said mammal a pharmaceutical effective amount of a composition comprising:

(a) an effective amount of one or more of acetylcholinesterase inhibitor(s) or a phamaceutically effective salt thereof

and

(b) an effective amount of one or more NMDA- antagonist(s)

13. The method of claim 11 wherein component (a) and component (b) are administered simultaneously.

14. The method of claim 11 wherein component (a) and component (b) are administered concomitantly.

15. The method of any of claims 11-13 wherein the dementia is of Alzheimer's type.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00342

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/55, A61K 31/13, A61P 25/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, EMBASE, MEDLINE, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	International Clinical Psychopharmacology, Volume 18, No 2, 2003, Susanne Hartman et al, "Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy", page 81 - page 85, 18 February 2003 --	2-4,9-11
X	Acetylcholinesterase Inhibitors vs. Memantine, Volume 66, No 12, 2000, Gary L. Wenk et al, "NO INTERACTION OF MEMANTINE WITH ACETYL CHOLINESTERASE INHIBITORS APPROVED FOR CLINICAL USE" page 1079 - page 1083 -- --------	2-4,9-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2003	25 -08- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Susanna Lindfors/MP Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK03/00342

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,5-8,12-15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Present claims 1, 5 - 8 and 12 - 15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small portion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to claims 2 - 4 and 9 - 11.